R_{10} is hydrogen or forms an alkylene chain together with R_3; and

J3 cont

R_{11} and R_{12} are the same or different and selected from the group consisting of hydrogen, halogen or alkyl,

with the proviso that the H^+, K^+-ATPase inhibitor is not pantoprazole.

REMARKS

I. Examiner Interview

Applicants and the undersigned Attorney wish to take this opportunity to thank the Examiner for the courtesy of the telephonic interview of 12 February 2003. The substance of the interview is summarized by the Interview Summary, mailed 13 February 2003.

II. Claim Amendments

Claim 3-11 and 19 have been cancelled. Upon entry of this Amendment, claims 1, 2, 18, 26 and 27 are pending. The pending claims are directed to the embodiment of original claim 3, now cancelled. Moreover, the amended claims have been re-written in Jepson format. The claim amendments are fully supported by the application as originally filed. Therefore, no new matter has been introduced.

The claims have been further amended by deleting the non-elected species (Groups II-IV) as summarized in the Office Action, mailed 30 April 1999 (Paper No. 5). This same amendment was made in the Amendment, mailed 23 July 2001, but the non-elected subject matter was mistakenly and inadvertently re-introduced in the Amendment, mailed 15 August 2002.

Applicants submit that none of the claim amendments was done in acquiescence of any objection or rejection relating to patentability. Rather, the claims were canceled and amended to advance the application to allowance so that Applicants may enjoy the benefits, without delay, conferred by a U.S. patent for allowable subject. Applicants reserve the right to file one or more divisional and/or continuation applications to defend the patentability of patentable subject matter that may have been removed by the claim amendments.

Applicants further submit that it is not necessary to amend the inventorship pursuant to 37 C.F.R. §1.48(b) in view of the claim amendments. Each of the currently named inventors is an inventor of at least one of the pending claims.

III. The Claimed Invention

The amended claims are directed to the embodiment of the Example, at pages 10-11, and Figure 1. As described in the Example, the pharmacological effect of the claimed invention was compared with a conventional administration regimen involving omeprazole. Pursuant to the invention, a first group of subjects received 20 mg of omeprazole twice daily with 3 hours apart from each administration. A second group of subjects received a single 40 mg daily dose of omeprazole. With each group of subjects, the efficacy of the respective administration regimen in controlling acid secretion was measured. As shown in Figure 1, the therapeutic effect of omeprazole is maximized, particularly on "day 1", when the blood plasma concentration of the drug is extended by repeated doses of omeprazole which are administered with 3 hours apart from each administration.

This improvement is defined by the pending claims which have been written in Jepson format. The Interview Summary provides that a Declaration under 37 C.F R. §1.132 is required

to support the improvement. Applicants respectfully submit, however, that the improvement defined by the pending Jepson claims is fully supported by the Example and Figure 1. Accordingly, in view of the fact that the pending claims are directed to the embodiment disclosed by the Example and Figure 1, a §132 declaration would be superfluous.

The novelty and nonobviousness of the claimed invention can be demonstrated by the following illustration:

PRIOR ART	CLAIMED INENVTION
DURATION OF ACID INHIBITION OF A ***SINGLE DOSE*** OF OMEPRAZOLE **3-4 DAYS**	***TWO CONSECUTIVE DOSES***, OR MORE, OF OMEPRAZOLE **0.5-4 HOUR INTERVALS**

Since it was known in the prior art that the duration of acid inhibition of a single dose of omeprazole is **3-4 days**, it was truly unexpected that the blood plasma level of omeprazole could be extended by two or more consecutive administrations with **0.5-4 hour intervals**. The unexpected improvement is shown by Figure 1. As such, the prior art is silent and shows no appreciation of the possibility of achieving an improvement by two or more consecutive administrations of an acid labile H^+, K^+-ATPase inhibitor with 0.5-4 hour intervals to extend the blood plasma level.

IV. Claim Rejection – 35 U.S.C. §112

Claims 1, 18, 26 and 27 are rejected under 35 U.S.C. §112 second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants submit that the claim amendments overcome the §112 rejection. As amended, the claims define an improved method for inhibiting gastric acid secretion The improvement is characterized by two or more consecutive administrations of an acid labile H^+, K^+-ATPase inhibitor with 0.5-4 hour intervals between administrations. Unexpectedly, the improvement results in an advantageous extension of the blood plasma level of the acid labile H^+, K^+-ATPase inhibitor.

Accordingly, the amended claims clearly explain the claimed improvement and the method for achieving the improvement. Withdrawal of the §112 rejection is requested.

V. Claim Rejection – 35 U.S.C. §102

The Office Action at page 3 provides that 1-11, 15, 16, 18, 19, 26 an 27 are rejected under 35 U.S.C. §102(b) in view of Martindale: The Extra Pharmacopoeia 13th Ed. (1993) ("Martindale"). Applicants wish to remind the Examiner that claims 15 and 16 were canceled by the Amendment, mailed 23 July 2001. Therefore, the pending claims are claims 1-11, 18, 19, 26 and 27 as correctly indicated on page 1 of the Office Action.

1. ***Increasing*** blood plasma level, as disclosed by Martindale, is not the same as ***extending*** blood plasma level, as claimed.

Martindale discloses that it may be possible to ***increase*** the blood plasma level of omeprazole by ***increasing*** the dosage. Applicants submit, however, that ***increasing*** the blood plasma level is not the same as ***extending*** the blood plasma level. Martindale does not teach or suggest that the blood plasma level of omeprazole can be ***extended*** by consecutive doses separated by 0.5-4 hour intervals. As discussed in Section III, above, the known prolonged

duration of acid inhibition of omeprazole, e.g., 3-4 days, offered no motivation, at the time the claimed invention was made, to administer tw consecutive doses of omeprazole separated by 0.5-4hour intervals to ***extend*** the blood plasma level.

2. The weight of Martindale is ***"once daily"*** dose of omeprazole.

Furthermore, Martindale discloses that the prolonged duration of acid inhibition of omeprazole allows it ***"to be used in single daily doses"*** and that ***"[t]he usual dose*** for healing oesophagitis is 20 to 40 mg ***once daily*** for 4 to 8 weeks; thereafter maintenance therapy can be continued with 20 mg ***once daily."*** Martindale recommends ***"a single daily dose"*** of 20mg or 40 mg in the management of peptic ulcers. As such, Martindale does not teach two consecutive doses of omeprazole separated by 0.5-4 hour intervals to inhibit gastric acid secretion.

Martindale also teaches ***"once daily"*** doses of 20 mg to 120 mg in the treatment of Zollinger-Ellison syndrome. However in the exceptional case, Martindale recommends that doses above 80 mg may be divided and given twice daily. Applicants respectfully submit that the disclosure of this limited exception does not arise to the level of a teaching as required by 35 U.S.C. §102. In fact, when the entirety of the Martindale reference is considered, the weight of the teaching by Martindale is ***"a single daily dose"***. Moreover, Martindale does not disclose, either expressly or inherently, the recited feature of two or more consecutive doses at 0.-5 to 4 hour intervals.

For all of the foregoing reasons, Martindale does not anticipate the claimed invention. Withdrawal of the §102 rejection is requested.

VI. Claim Rejection – 35 U.S.C. §103

The Office Action provides that claims 1-11, 15, 16, 18-21 and 23-25 remain rejected under 35 U.S.C. §103 in view of US 5,330,982 to Tyers ("Tyers") for the reasons of record. Applicants wish to remind the Examiner that claims 15 and 16 were cancelled by the Amendment, mailed 23 July 2001. Therefore, the pending claims are claims 1-11, 18, 19, 26 and 27 as correctly indicated on page 1 of the Office Action.

1. Tyers discloses a combined dosage form comprising a 5-HT receptor antagonist and a H^+, K^+-ATPase inhibitor and a separate dosage form for each of the two therapeutic agents.

Applicants acknowledge that Tyers discloses a combination therapy comprising a 5-HT receptor antagonist and a H^+, K^+-ATPase inhibitor. At column 2, lines 60-66, Tyers provides that the 5-HT receptor antagonist and a H^+, K^+-ATPase inhibitor may be administered as a single dosage form or as two separate dosage forms for simultaneous or sequential use.

2. Tyers disclose an administration regime of 1 to 4 times a day for the a 5-HT receptor antagonist but not for the H^+, K^+-ATPase inhibitor.

It is Applicants' position that the administration regimen appearing in column 9 of Tyers relates only to the separate dosage form consisting of the 5-HT receptor antagonist. In general, Tyers provides that a unit dose of the 5-HT receptor antagonist of Formula I-VIII (See cols. 3-7) can be administered 1 to 4 times a day. However, there is nothing to suggest that this same administration regime, i.e., 1 to 4 times a day, also applies to the H^+, K^+-ATPase inhibitor. For example, the Examiner's attention is directed to the following disclosure at column 9, lines 8-13:

> Thus a composition for use according to the invention containing ***a compound of formula (I)*** as herein defined may contain 0.2 to 250 mg of ***the active ingredient*** per unit dose, any may be administered for example up ***four times per day***, such that the overall daily dose is in the range 0.5 to 500 mg. (Emphasis added)

There is only one reasonable interpretation of the above disclosure from Tyers. The composition is a separate dosage form consisting of the 5-HT receptor antagonist of the Formula (I) as the active ingredient. It is this active ingredient which Tyers discloses may be administered 1 to 4 times a day. There is nothing to suggest that the same frequency "1 to 4 times per day" applies to the H^+, K^+-ATPase inhibitor in combination with the 5-HT receptor antagonist or as a separate dosage form.

Thus, without the benefit of impermissible hindsight, it is not possible to find any support for the Examiner's position that Tyers discloses the administration of the H^+, K^+-ATPase inhibitor 1 to 4 times a day. Similar to the Martindale disclosure, Tyers is directed to the conventional practice of administering ***"once daily"*** doses of the H^+, K^+-ATPase inhibitor. For all of the foregoing reasons, there is no suggestion or motivation offered by Tyers to administer the H^+, K^+-ATPase inhibitor at 0.5-4 hour intervals. Moreover, there is no suggestion that it would be possible to advantageously extend the blood plasma profile by administering the H^+, K^+-ATPase inhibitor at 0.5-4 hour intervals.

Withdrawal of the §103 rejection based on Tyers is requested.

VII. Claim Rejection – 35 U.S.C. §103

Claims 1-11, 15, 16, 18, 19, 26 and 27 are rejected under 35 U.S.C §103(a) in view of the combination of WO 96/01624 and Tyers. Applicants wish to remind the Examiner that claims 15 and 16 were canceled by the Amendment, mailed 23 July 2001.

According to the Examiner, WO 96/01624 at page 10, lines 17-22, discloses that dosage forms comprising a proton pump may be administered one to several times a day and that the daily dose will be in the range of 1-1000 mg. The Examiner relies on the alleged disclosure by Tyers of an administration regime of 1 to 4 times a day. The Examiner concludes that it would have been obvious at the time the claimed invention was made to combine WO 96/01624 and Tyers to arrive at the claimed invention.

The primary reference WO 96/10624 is directed to a multiple unit formulation comprising a H^+, K^+-ATPase inhibitor, wherein the individual units are coating layered with an enteric coating having certain mechanical properties (See claim 1 at page 36). Applicants submit that the administration regimen as broadly disclosed by WO 96/01624, i.e , daily doses one to several times a day, is consistent with the typical administration regimen of pharmaceuticals. In this regard, Applicants rely on the cited prior art reference to Martindale which teaches the administration of ***a single daily dose*** of omeprazole.

Therefore, the disclosure by WO 96/01624 of more than a single daily dose relates to the exceptional case, e.g., in the treatment of Zollinger-Ellison syndrome, when higher doses are required. For example, Martindale discloses that the initial recommended dosage for patients with the Zollinger-Ellison syndrome is 60 mg ***once daily***. However, when treatment of the syndrome requires a higher daily dose, Martindale suggests that doses above 80 mg should be divided and given twice daily, for instance, one morning and one evening dose. Notwithstanding this limited disclosure relating to an exceptional instance, there is no suggestion by WO 96/01623 of the claimed method of administering two or more consecutive unit doses of an H^+, K^+-ATPase inhibitor with 0.5-4 hour intervals to obtain a different and improved therapeutic effect.

With respect to the secondary reference to Tyers, Applicants rely on their remarks in Section VI, above. Specifically, although Tyers may disclose that a unit dose of the 5-HT receptor antagonist of Formula I-VIII can be administered 1 to 4 times a day, there is nothing to suggest that this same administration regime, i.e., 1 to 4 times a day, also applies to the H^+, K^+-ATPase inhibitor.

Therefore, whether taken alone or in combination, WO 96/01624 and Tyers fail to suggest the claimed invention. Neither reference provides the required motivation to suggest consecutive dosages separated by 0.5-4 hour intervals to advantageously obtain an extended blood plasma profile of an H^+, K^+-ATPase inhibitor.

Withdrawal of the §103 rejection based on the combination of WO 96/01624 and Tyers is requested.

Serial No.: 08/945,425
Filed: October 21, 1997

CONCLUSION

The claim amendments and remarks set f rth herein are fully responsive to the Office Action. It is respectfully submitted that claims 1, 2, 18, 26 and 27 are in condition for allowance, which action is earnestly solicited.

Any additional fee in connection with this response should be charged to Deposit Account No. 23-1703.

Dated: April 8, 2003

Respectfully submitted,

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Reg. No. 32,224
Attorney for Applicants

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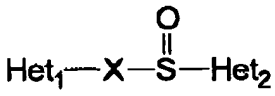
Mark-up copy of amended claims 1, 2, 18, 26 and 27 showing insertions and deletions:

1. (Five times amended) In a [A] method of treatment for improving the inhibition of gastric acid secretion which consists of [comprises] administering to a host in need thereof an oral pharmaceutical formulation comprising a therapeutically effective amount of an acid labile H^+, K^+-ATPase inhibitor, the improvement characterized by:

extending the [wherein the method induces an extended] blood plasma profile level of the H^+, K^+-ATPase inhibitor by two or more consecutive oral administrations of a unit dose of [, and] the H^+, K^+-ATPase inhibitor with 0.5 – 4 hour intervals,

wherein the H^+, K^+-ATPase inhibitor is a compound of the formula I



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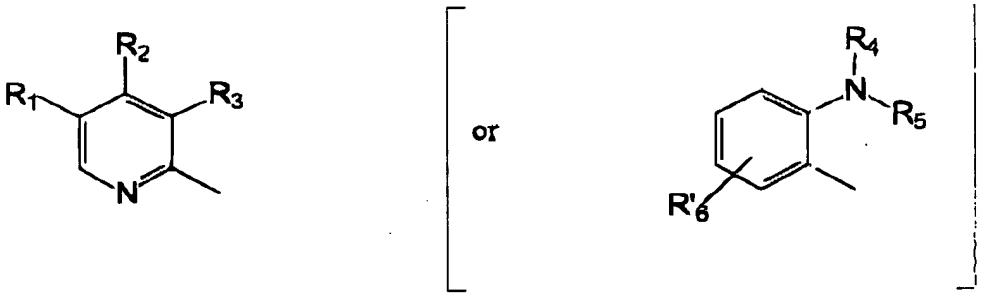

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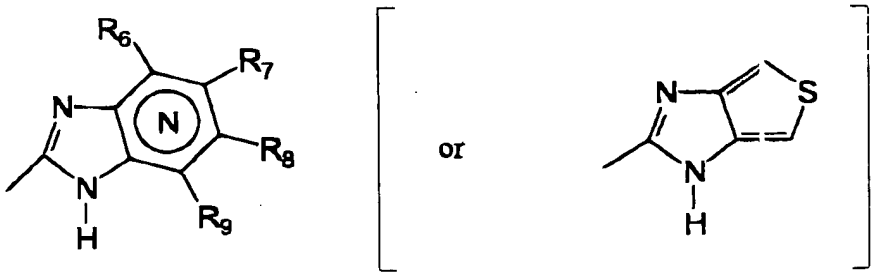

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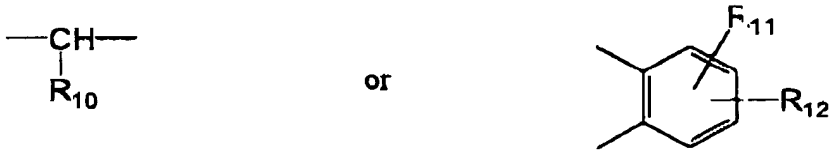


wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_6-R_9 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3; and

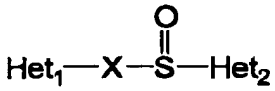
R_{11} and R_{12} are the same or different and selected from the group consisting of hydrogen, halogen or alkyl.

2. (Amended) The method according to any one of claims 1, 18, 26 or 27 [1 or 26], wherein the H^+, K^+-ATPase inhibitor is a compound selected from the group consisting of omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole and an alkaline alt of the (-)-enantiomer of omeprazole.

18. (Four times amended) In a [A] method of treatment for improving the inhibition of gastric acid secretion which consists of [comprises] administering to a host in need thereof an oral pharmaceutical formulation comprising a therapeutically effective amount of an acid labile H^+, K^+-ATPase inhibitor, the improvement characterized by:

extending the [wherein the method induces an extended] blood plasma profile level of the H^+, K^+-ATPase inhibitor by two or more consecutive oral administrations of a unit dose of [, and] the H^+, K^+-ATPase inhibitor with 0.5 – 4 hour intervals,

wherein the H^+, K^+-ATPase inhibitor is a compound of the formula I



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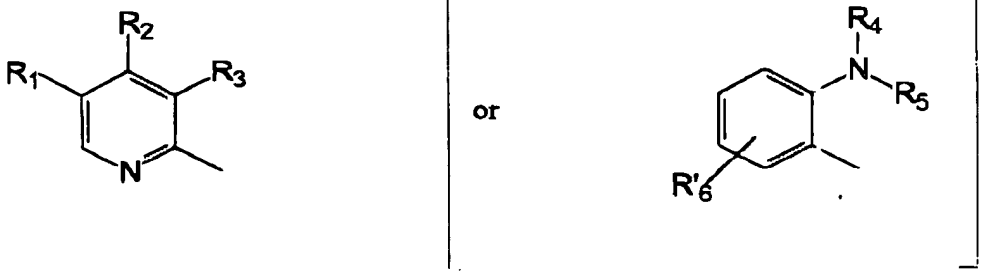

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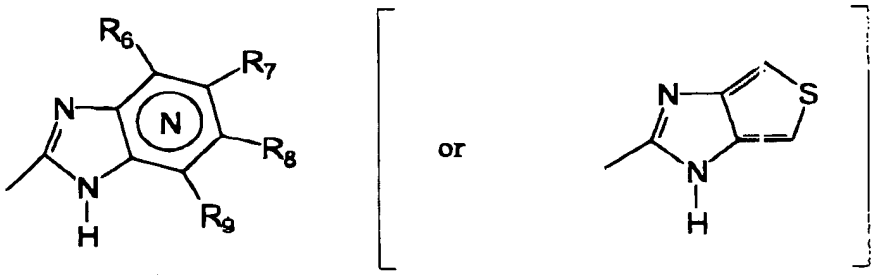

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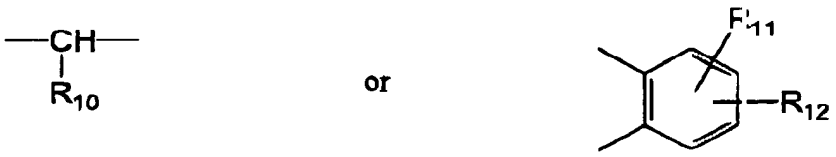


wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_6-R_9 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

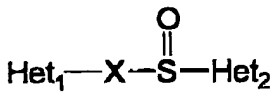
R_{10} is hydrogen or forms an alkylene chain together with R_3; and

R_{11} and R_{12} are the same or different and selected from the group consisting of hydrogen, halogen or alkyl
with the proviso that the H^+, K^+-ATPase inhibitor is not pantoprazole.

26. (Thrice amended) In a [A] method for improving the treatment of gastrointestinal disorders associated with excess acid secretion which consists of [comprises] administering to a host in need thereof an oral pharmaceutical formulation comprising a therapeutically effective amount of an acid labile H^+, K^+-ATPase inhibitor, the improvement characterized by:

extending the [wherein the method induces an extended] blood plasma level profile of the H^+, K^+-ATPase inhibitor by two or more consecutive oral administrations of a unit dose of [, and] the H^+, K^+-ATPase inhibitor with 0.5- 4 hour intervals,

wherein the H^+, K^+-ATPase inhibitor is a compound of the formula I



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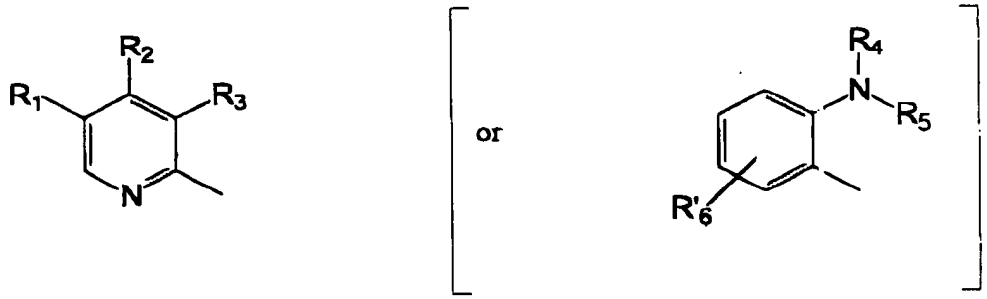

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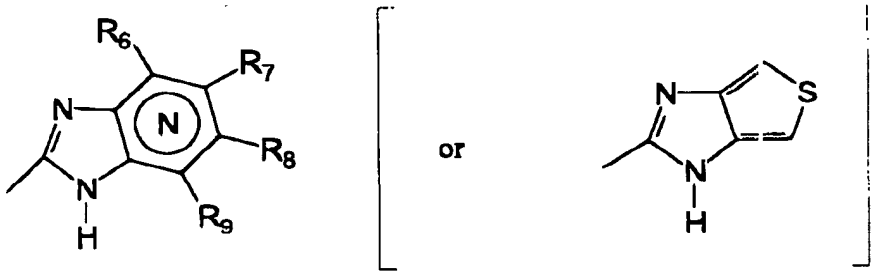

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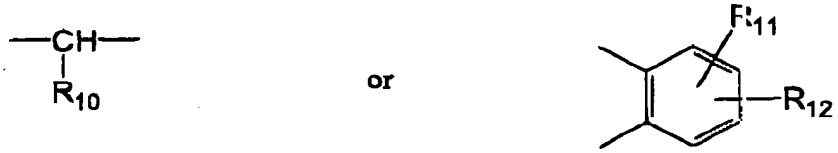

wherein

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R_1, R_2 and R_3 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_6-R_9 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

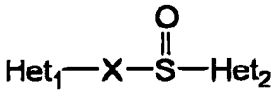
R_{10} is hydrogen or forms an alkylene chain together with R_3; and

R_{11} and R_{12} are the same or different and selected from the group consisting of hydrogen, halogen or alkyl.

27. (Thrice amended) In a [A] method for improving the treatment of gastrointestinal disorders associated with excess acid secretion which consists of [comprises] administering to host in need thereof an oral pharmaceutical formulation comprising a therapeutically effective amount of an acid labile H^+, K^+-ATPase inhibitor, the improvement characterized by:

extending the [wherein the method induces an extended] blood plasma profile of the H^+, K^+-ATPase inhibitor by two or more consecutive oral administrations of a unit dose of [, and] the H^+, K^+-ATPase inhibitor with 0.5-4 hour intervals,

wherein the H^+, K^+-ATPase inhibitor is a compound of the formula I



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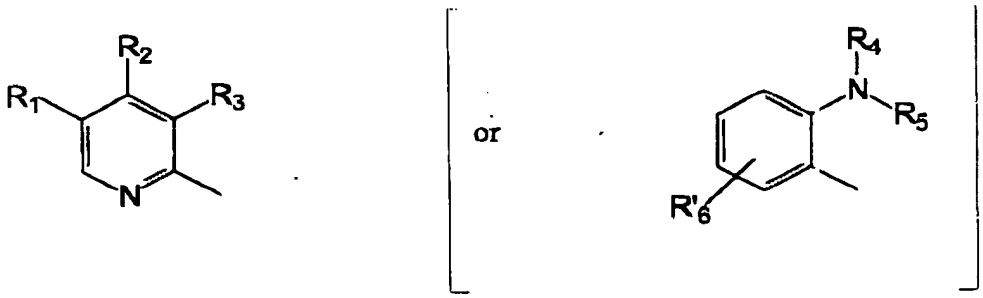

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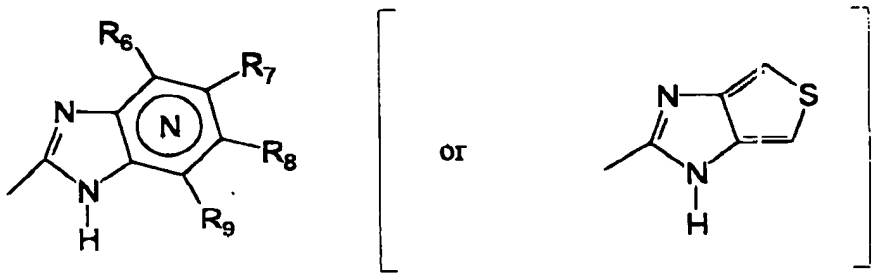

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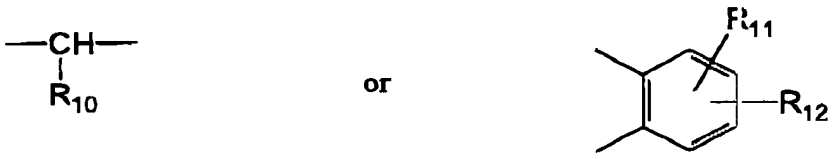

wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, fluorine-substituted alkoxy, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_6-R_9 are the same or different and selected from the group consisting of hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3; and

R_{11} and R_{12} are the same or different and selected from the group consisting of hydrogen, halogen or alkyl,

with the proviso that the H^+, K^+-ATPase inhibitor is not pantoprazole.